

# The Impact of Winter Epidemics of Influenza and Respiratory Syncytial Virus on Paediatric Admissions to an Urban General Hospital

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To demonstrate the impact of influenza epidemics on pediatric hospital admissions, admissions that were attributable to influenza and respiratory syncytial virus (RSV) infection to the pediatric ward of an urban general hospital in Japan were followed-up during a 4-month period from December to March 1991 through 1998. During the 1997–1998 influenza type A (H3N2) epidemic, a diagnosis of influenza type A (H3N2) was made in 26.3% of all patients admitted aged 15 years or lower. During the peak of the epidemic, as many as 50–70% of the admissions were attributable to influenza type A (H3N2). In the seven winters from 1991 to 1988, 14.0% of all admissions were associated with infection with influenza virus (mean age 4.4 years), and 17.5% were due to RSV. More patients were admitted to hospital for influenza than RSV infection in three of the seven seasons. Among the patients with influenza, 74.5% of the cases were previously healthy children. Influenza and RSV infection are leading causes of pediatric hospital admissions during the winter. Effective methods of prophylaxis are needed not only for high-risk patients, but for healthy young children. *J. Med. Virol.* 60: 102–106, 2000. © 2000 Wiley-Liss, Inc.

**KEY WORDS:** children; rapid diagnosis; influenza virus; respiratory syncytial virus

## INTRODUCTION

It has been reported that schoolchildren and children attending day care centers are the principal transmitters of influenza in the community and the introducers of the virus into the household [Glezen, 1980; Jennings and Miles, 1978]. However, influenza in children does not generally produce excess mortality [Glezen, 1980]. In one study, excess hospitalization rates among children ages 0–14 year during epidemics were only one-fifth the rate of persons over the age 65 years [Mullooly and Barker, 1982]. On the other hand, influenza does cause excess mortality and hospitalization in elderly

people [Lui and Kendal, 1987], and as a result, immunization with influenza vaccine is recommended for elderly people in most developed countries [Fedson et al., 1995].

It has been reported previously that influenza exceeded respiratory syncytial virus (RSV) infection as a cause of pediatric hospitalization during a severe influenza epidemic, and most of the influenza patients were previously healthy children [Sugaya et al., 1992]. However, only a few reports demonstrating the significance of influenza as a cause of pediatric hospitalization have been published [Glezen et al., 1980; Sugaya et al., 1992]. By contrast, it is well documented that RSV is the single most important lower respiratory tract pathogen in children [Anderson et al., 1990], and an RSV vaccine has recently been developed [Crowe, 1995; Murphy and Collins, 1997].

Although safe and effective influenza vaccine is available, influenza immunization has not been recommended for healthy young children, mainly because the importance of influenza virus infection as a cause of pediatric hospitalization has not been fully understood. The purpose of this study was to demonstrate the impact of influenza epidemics on pediatric hospital admissions, as compared with RSV outbreaks.

## MATERIALS AND METHODS

### Patients

Nippon Kokan Hospital (Kawasaki, Japan) is a 395-bedded hospital with 32 pediatric beds, excluding a neonatal intensive care unit. Infants and children aged 15 years and younger are admitted to the pediatric ward.

The period of the study was the seven winter seasons from 1991–1998. During the 4-month period from December to March each year, paired serum samples were obtained from all children at the time of admission and

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10 to 14 days later. The samples were used to measure acute and convalescent complement fixation (CF) titres for influenza A and B virus, adenovirus, RSV, and *Mycoplasma pneumoniae*, plus the hemagglutination inhibition (HI) titres for influenza A (H1N1, H3N2) and B virus, and parainfluenza virus types 1–3. The haemagglutinin antigens of the influenza viruses were the antigens of the vaccine strains used that season. Patients who were thought to have been infected nosocomially were excluded from this study, even if significant rises in antibody titre had occurred. From 1991 to 1997, 10 to 20 samples were obtained each season to isolate influenza virus and characterize the epidemic strains.

Nasotracheal aspirates from patients aged 2 years and younger who had respiratory symptoms were examined for RSV antigen by enzyme immunoassay (EIA) on admission, and stool samples from all children with diarrhoea in this age group were assayed for rotavirus antigens.

During the 1997–1998 season, nasotracheal aspirates were examined for influenza type A antigen by a rapid antigen detection test using EIA (Directigen Flu A, Becton Dickinson, Franklin Lakes, NJ) on admission for all patients with a fever higher than 37.5°C associated with lower respiratory tract signs (rhonchi, rales) and upper respiratory tract signs (rhinorrhoea, cough). The same samples were used for isolation of influenza viruses with MDCK cells.

## METHODS

During the six seasons from 1991 to 1997, influenza virus infection was diagnosed when a four-fold or greater rise in HI antibody titres of influenza virus was detected (197 cases), and 27 of the patients were also positive by viral isolation. In addition, during the 1997–1998 season, influenza type A (H3N2) infection was diagnosed in a total of 77 patients mainly by the rapid antigen detection test and isolation. Thus, the total number of patients with influenza was 274.

Patients whose HI influenza antibody titres virus were significantly increased, but who were also demonstrated to be positive for RSV antigen by EIA on admission were classified as RSV patients (9 cases).

RSV infection was diagnosed when RSV antigen was positive by EIA on admission or when RSV CF titres increased four-fold or more. Most were diagnosed by RSV antigen testing by EIA on admission (325 cases). RSV infection was also diagnosed in patients aged 3 years and younger who were not tested for RSV antigen by EIA and who showed a 4-fold or greater rise in RSV CF antibody (18 cases). Thus, the total number of RSV cases was 343.

## RESULTS

Figure 1 shows changes in the proportions of influenza virus and RSV in hospitalised patients during the 4-month period from December 1997 to March 1998. During this period, a total of 293 children were admitted, including 77 patients with influenza type A (H3N2) infection (26.3%, 77/293). Influenza type A

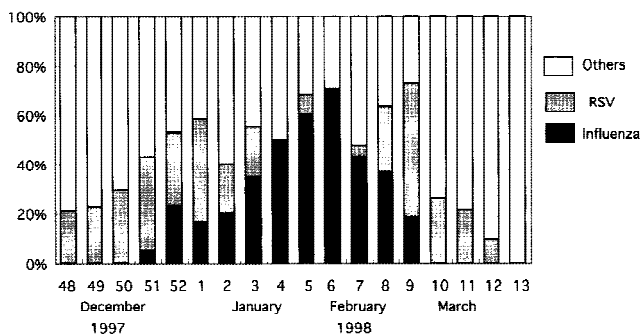


Fig. 1. Changes in proportions of hospitalized patients with influenza type A (H3N2) virus and respiratory syncytial virus (RSV) from December 1997 to March 1998 (weekly).

(H3N2) was confirmed by all three tests, i.e., by culture, the rapid antigen test, and the HI test, in 42 of the 77, by both the rapid test and the HI test in 9, by both culture and the rapid test in 6, by both culture and the HI test in 2, by either culture or the rapid antigen test in 5, and by the HI test alone in 13. The strains isolated were all influenza type A (H3N2) virus, and further analysis of 12 strains demonstrated that 10 were A/Sydney/5/97-like strains and the other 2 were A/Wuhan/359/95-like strains. During the same period, 56 patients with RSV were admitted (19.1%, 56/293).

The first patient with influenza type A (H3N2) was admitted on December 19, 1997, and pediatric admissions with influenza type A (H3N2) gradually increased thereafter (Fig. 1). In the 6th week of 1998, 70.4% of the all admissions were patients with influenza type A (H3N2) and during the 4th–6th weeks, influenza type A (H3N2) accounted for more than 50% of all admissions to the pediatric ward. During this period, the number of patients with RSV decreased markedly.

The mean total pediatric admissions during the 4-month period (December to March) in the 7 seasons from 1991–1998 was 280 (range 252 to 309) (Table I). The mean number of patients with influenza was 39.1, or 14.0% of the total pediatric admissions, versus 49.0 with RSV, or 17.5% of the total pediatric admissions. In 3 of the 7 seasons, 1992–1993, 1994–1995, and 1997–1998, which coincided with the occurrence of major epidemics in Japan, the patients with influenza exceeded those with RSV. Influenza type A (H3N2) was predominant among the influenza patients (62.0%, 170/274). Except for rotavirus infection (21.9 cases, or 7.8% of the total pediatric admissions), there were fewer than five cases each of infection by other agents (*Mycoplasma pneumoniae*, adenovirus, and parainfluenza virus) (Table I).

Figure 2 shows age distributions of patients with influenza and RSV infection. The mean age of influenza patients was 4.4 years (median 3.4, interquartile range 3.9), and the patients admitted were mainly young children, with peaks at 1–2 years old. The number of infants (<1 year) was half the number of 1 year old children (25 vs. 51). On the other hand, the mean age of the

TABLE I. Hospitalized Patients With Influenza, Respiratory Syncytial Virus Infection, and Other Infections During the 4-Month Winter Period (December to March) From 1991 Through 1998

	1991-92	1992-93	1993-94	1994-95	1995-96	1996-97	1997-98	Total	Mean
A (H1N1)	18	1	0	2	12	0	0	33	4.7
A (H3N2)	1	10	25	23	1	33	77	170	24.3
B	0	39	0	18	0	14	0	71	10.1
Influenza (total)	19	50	25	43	13	47	77	274	39.1
RSV	40	23	52	40	67	65	56	343	49.0
Rotavirus	20	26	29	29	19	21	9	153	21.9
<i>M. pneumoniae</i>	4	7	2	1	6	10	5	35	5.0
Adenovirus	1	2	3	8	4	2	2	22	3.1
Para-3	1	1	0	2	1	0	0	5	0.7
Total admissions	252	275	272	272	286	309	293	1959	280.0

A (H3N2): influenza type A (H3N2); A (H1N1): influenza type A (H1N1); B: influenza type B; RSV: respiratory syncytial virus; *M. pneumoniae*: *Mycoplasma pneumoniae*; Para-3: parainfluenza virus type 3.

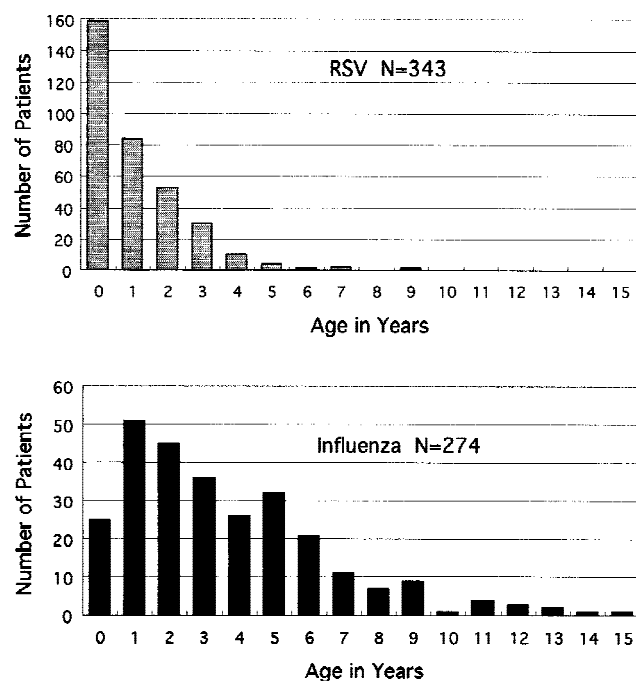


Fig. 2. Age distribution of hospitalized patients with influenza (lower) and with respiratory syncytial virus (upper) from 1991 through 1998.

patients with RSV infection was 1.6 years (median 1.1, interquartile range 1.7) and infants (<1 year) accounted for as high as 46.4% (159/343).

Seventy of the 274 patients (25.5%) with influenza had underlying diseases, and as many as 64 of the 70 had asthma. Three of the other 6 patients had epilepsy, one had congenital heart disease, one had hydronephrosis, and one had nephrotic syndrome. The other 204 influenza patients (74.5%) were otherwise healthy children.

Five of the 274 influenza patients (four with influenza type A (H3N2) and one with influenza type B) had received influenza vaccine before the epidemic.

Every patient was examined by chest x-ray on admission. Bronchitis was diagnosed on the basis of lower respiratory tract signs (rhonchi, rales) with normal chest x-ray findings. Pneumonia was diagnosed on the

basis of lower respiratory tract signs plus an infiltrate on the chest x-ray. Of the 274 children with influenza, 150 were admitted for bronchitis (81 cases) or pneumonia (69 cases) and 15 for laryngitis. Thus, about 60% were admitted because of lower respiratory infection (60.2%, 165/274). The pneumonia was mild clinically, and not associated with bacterial infection in most cases.

Seventy-three were diagnosed as having pharyngitis, but their complaints were variable, and included persistent fever to rule out sepsis, dehydration, lethargy, and so forth. Fifteen had asthmatic attacks, 14 were hospitalized because of febrile convulsions, and 7 had gastroenteritis. No deaths occurred during the study.

## DISCUSSION

Although the annual average number of admissions for influenza was less than for RSV infection (39.1 vs. 49.0), the number of influenza patients exceeded the number with RSV infection in the years of influenza epidemics (Table I). The results demonstrate that the impact of an influenza epidemic on pediatric hospitalization is much greater than generally thought. During the 1997-1998 season, the largest epidemic in Japan in the last ten years, more than 50% of the admissions for three consecutive weeks were for influenza type A (H3N2) (Fig. 1). A similar experience was reported during the 1989-1990 epidemic [Sugaya et al., 1992]. Although this study was based on data obtained in the pediatric ward of a general hospital in Japan, the impact of influenza epidemics on children is probably similar in all developed countries.

Winter et al. [1996] reported the incidence of respiratory viruses identified in children admitted to a children's hospital. Their data showed 10 times more RSV patients than influenza patients, suggesting that the impact of influenza on children was much less than in the present study. Because Winter et al. [1996] reported on a children's hospital, patients with moderate to severe RSV infection may have been selected and collected for intensive respiratory care in that hospital. The discrepancy may also be attributable to the differences in the sensitivity of diagnostic methods for influenza.

Figure 1 shows that when the influenza patients ap-



peared, those with RSV, who had accounted the majority of pediatric patients, clearly decreased. Glezen et al. [1973, 1980] reported that at the peak of epidemics, influenza viruses appeared to interfere with the spread of other major respiratory viruses, particularly RSV, and Norwegian data have supported the belief that interference occurs between outbreaks of RSV infection and influenza, making it impossible for both viruses to reach the peaks of their epidemics during the same period [Anestad, 1982; Anestad, 1987].

Most hospitalized influenza patients were infants and young children aged 6 years or younger, not school children more than 7 years old (Fig. 2). The number of infants (<1 year) with influenza was characteristically about half the number of 1 year olds. By contrast, infants predominated among children with RSV infection (Fig. 2). Infants may be protected from influenza virus infection by passive maternal antibody [Reuman et al., 1987].

Most of the influenza patients were healthy and had no underlying disease (74.5%). Asthma predominated among the patients who had an underlying disease, mainly because we treated only a small number of patients with heart disease, renal disease, or other chronic illnesses. Also, asthma patients may be much more susceptible to influenza virus infection, although only 23.4% of them had severe asthmatic attacks during their hospital stay.

The limitations of this study should be recognized. Except for the 1997–1998 epidemic caused by influenza type A (H3N2), most influenza patients were diagnosed only on the basis of HI tests with paired sera. The HI test was confirmed to be a reliable diagnostic method during the 1997–1998 epidemic, and showed about 80% to 90% sensitivity and specificity compared to the rapid antigen test and culture [Mitamura et al., 1998]. Therefore, although slightly less sensitive, the HI test was not a major drawback to the diagnosis of influenza type A infection in this study. On the other hand, HI antibody has been reported to be unreliable as a means of establishing that influenza type B infection had occurred [LaMontagne, 1980]. Therefore, a moderate number of influenza type B patients may have been undiagnosed.

The impact of influenza epidemics on pediatric hospitalization has obviously been underestimated. This is because it is more difficult to diagnose influenza in children than RSV infections. Most patients with RSV infections are infants, and their characteristic symptom is wheezing. Moreover, a rapid EIA test for RSV is widely used. In contrast, influenza virus infections show a variety of clinical manifestations other than respiratory symptoms [Glezen, 1980; Sugaya et al., 1992], and the patients' age range is wider. In addition, rapid diagnosis for influenza at the bedside is not used commonly. As a result, pediatricians may often miss influenza virus infections.

This study demonstrated that influenza, as well as RSV, are leading causes of pediatric hospitalization during the winter season. We believe that effective

methods of prophylaxis should be developed not only for elderly people, but also for healthy young children. Based on the data obtained in this study, influenza vaccine should be recommended for children 1–6 years old.

It was reported that during the 1992–1993 epidemic, protection against markedly drifted influenza type A (H3N2) was 53.5% in young children [Sugaya et al., 1994]. Immunization with the current inactivated vaccine is a sufficiently effective method for protecting young children and has greatly reduced the number of hospitalized children, because most hospitalized influenza patients have been infected with influenza type A (H3N2). However, there are several problems in immunizing young children with current inactivated vaccines. In addition to concern about adverse effects, inactivated vaccines that require parenteral administration will probably be impractical, particularly if yearly administration of one or two doses is necessary [Glezen, 1980]. At present, live influenza vaccine is being tested in the United States [Belshe et al., 1998], and thus far it has shown promise of efficacy. When it becomes possible to use live influenza vaccine in actual practice, wider immunization of healthy young children should be discussed.

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